Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Meta-trial of awake prone positioning with nasal high flow therapy: Invitation to join a pandemic collaborative research effort

Jie Li [a], Ivan Pavlov [b], John G. Laffey [c,h], Oriol Roca [d,i,j], Sara Mirza [e], Yonatan Perez [f], Bairbre McNicholas [c,h], David Cosgrave [c,h], David Vines [a], Elsa Tavernier [g,k], Stephan Ehrmann [f,l,*]

[a] Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, IL, United States of America
[b] Department of Emergency Medicine, Hôpital de Verdun, Montréal, Québec, Canada
[c] Anaesthesia and Intensive Care Medicine, School of Medicine, National University of Ireland Galway, Ireland
[d] Servei de Medicina Intensiva, Hospital Universitari Vall d'Hebron, Institut de Recerca Vall d'Hebron, Barcelona, Spain
[e] Division of Pulmonary and Critical care, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, United States of America
[f] CHRU Tours, Médecine Intensive Réanimation, CIC INSERM 1415, REVA and CRICS-TriggerSEP Research Networks, Tours, France
[g] Universities of Tours and Nantes, INSERM 1246-SPHERE, Tours, France
[h] Department of Anaesthesia, University Hospital Galway, Saolta Hospital Group, Ireland
[i] Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain
[j] Ciber Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[k] Clinical Investigation Center, INSERM 1415, CHRU Tours, Tours, France
[l] INSERM, Centre d'étude des Pathologies Respiratoires, U1100, Université de Tours, Tours, France

1. Introduction

The ongoing coronavirus disease pandemic (COVID-19) poses a great challenge to healthcare systems worldwide. Beyond challenges for direct patient care, optimal conduct of research under the specific conditions of the pandemic is a matter of concern and discussion. We present the *meta-trial* concept as a scientifically, clinically, ethically and socially sound method to carry out optimal clinical research in the setting of a pandemic. We take the example of such a *meta-trial*, set up to investigate prone positioning among awake patients undergoing nasal high flow therapy and invite journal readers to join this collaborative research effort.

2. COVID-19 constraints to clinical research

The pandemic has placed the research community under great pressure with the urgent need for results, given the lack of knowledge concerning optimal management of patients suffering this new disease. Public pressure is high due to the lack of specific effective therapy regarding this major threat to public health; the traditional pace of clinical research being considered as not adapted by most stakeholders. Worldwide funding agencies and regulatory bodies changed their procedures in order to speed up the research process. This effort has led to the launch of a high number of clinical studies within a short period of time to an unprecedented extent. As of 2020 June 15th, 2138 COVID-19 trials were registered in clinicaltrials.gov.

3. Pros/cons of national independent trials vs international trials

Numerous such trials launched simultaneously across hospitals in various countries address similar research questions. E.g. the search terms of "COVID AND Prone" to retrieve studies evaluating patient prone positioning on clinicaltrials.gov yielded 6, 31 and 44 results on the 5th of April, 5th of May and 5th of June respectively. This poses a major risk of redundant work, poor research resource allocation and incompletion of some trials – this happened all too often during previous epidemics [1-3]. Researchers may waste time writing protocols from scratch while others already obtained funding or regulatory approvals. Although data generated by these numerous trials may ultimately be meta-analyzed, the time required for these numerous individual trials to publish and then compile data may be incompatible with the pressure of the epidemic. Several stakeholders called for a coordinated research effort, which should ideally take place at the international level [1].

However, setting up an international trial requires tremendous resources and time to finalize a unique protocol translated in various languages, coordinate all regulatory and ethical approvals, and conduct trials and data quality assessment in each country [4,5]. Such efforts have been conducted successfully for observational studies with the support of international research networks and scientific societies [6]. However, the hurdles to set up a large scale international interventional randomized controlled trial are incompatible with the resources of an academic sponsor and are thus often restricted to pharmaceutical companies. When evaluating non-pharmacological interventions such as prone positioning, which has been proven to reduce mortality in mechanically ventilated patients with ARDS [7], the lack of foreseeable return on investment precludes such funding.

* Corresponding author at: Médecine Intensive Réanimation, CHRU de Tours, 2, Bd Tonnellé, 37044 Tours cedex 9, France.
E-mail address: stephanehrmann@gmail.com (S. Ehrmann).

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Table 1
Comparison of the meta-trial concept to alternative designs.

	Individual trials followed by a retrospective meta-analysis	International single trial	*Meta-trial*: prospective international meta-analysis
Eligibility criteria for participants	Heterogenous between trials	Uniform within the trial	Similar between trials (may have some heterogeneity within clinical relevance)
Baseline data	Heterogenous between trials	Uniform within the trial	Common set of variables in data sharing agreement
Intervention details and how they were administered	Heterogenous between trials	Uniform within the trial	Uniform between trials: agreement between individual investigators to deliver same intervention
Pre-specified primary and secondary outcome measures	Heterogenous between trials	Uniform within the trial	Uniform between trials (investigators agree on a common set of outcomes)
Samples size and Interim analysis	Heterogenous between trials, interim analyses impossible at the meta-level	One sample size calculation for the trial, interim analyses possible	Meta-trial design transcends original sample size calculation, interim analyses possible at the meta-level
Randomization- sequence generation, stratification, allocation sequence, concealment and blinding	Heterogenous between trials	Centralized randomization	May differ for each site but fundamental randomization principles adhered to
Statistical methods	Heterogenous original analyses, meta-analysis on effect sizes to compute a summary effect	Uniform within the trial, adjustments possible	Uniform within the trials, meta-analysis on individual participant data, adjustments possible
Analysis populations: intention to treat, Per protocol, subgroups	Heterogenous between studies	Uniform within the trial	Uniform between the trials (agreement on uniform analysis population)
Data quality and safety monitoring	Each trialist is responsible for his or her trial	Centralized data monitoring	Each trialist is responsible for his or her trial
Funding	Multiple funding	Centralized funding	Multiple funding
Set-up time	Short	Long	Short
Time to completion	Long	Short	Short
Protocols	Multiple original protocols	One	Multiple original protocols followed by a meta-trial protocol
Ethics	Each trialist is responsible for his or her trial	Centralized submission process	Each trialist is responsible for his or her trial

4. The *meta-trial* as a pragmatic solution for efficient pandemic clinical research

In order to combine the benefits of international research with the fast setup of national trials, we propose to coordinate multiple national investigator-initiated trials in the form of a prospective meta-analysis. This so-called "*meta-trial*" consists of aggregating data from various national trials during the data collection [8]. To study prone positioning in awake patients with COVID-19 pneumonia, two such trials were registered on clincaltrials.gov (one in the USA, the other in France) in mid-march 2020, and the investigators got in contact with 3 other groups planning trials with very similar inclusion and outcome criteria in Canada, Ireland and Spain, who all joined the *meta-trial* project. Each trial could be set up within a few weeks given the accelerated procedures in place during the COVID-19 outbreak. Planned sample sizes of individual trials ranged from 198 to 346 patients with the total planned inclusion of 1386 patients across 5 countries. Investigators and methodologists of all groups organized several web meetings to harmonize inclusion criteria and primary and secondary outcomes of the *meta-trial*. Given the planned sample sizes, an interim analysis plan was developed at the *meta-trial* level analyzing aggregated data every 200 patients. A memorandum of understanding and data sharing agreement were drafted (available upon request).

The *meta-trial* concept enables researchers to combine the agility of smaller national trials into a much larger international project in a short period of time (Table 1). *Meta-trial* interim analysis enables to detect a positive or negative response to the scientific question as soon as an adequate sample size is reached across several countries, thus potentially speeding up the research process dramatically [9,10]. Adherence to methodological standards of individual trials represents a guarantee of a high level of overall final quality. Furthermore, by estimating the treatment effect across the various trials upfront, the *meta-trial* may provide stronger evidence in favor of external validity and replicability of the individual trials.

To the best of our knowledge, the *meta-trial* concept has never been experienced in real life across several countries, and feasibility uncertainties do exist. The present project may serve as a guidance for future research projects set up in a pandemic context.

5. How to join

The *meta-trial* is a living project in the sense that other groups can join as long as they adhere to the general principle and abide by ethical regulations in their country. Protocols and clinical record files are made available upon request by the core investigator group of the *meta-trial*. Readers are invited to contact authors for any additional information and to join the project (Awake.Prone.Meta.Trial@gmail.com).

Authors contributions

ET, JL and SE initially designed the project, SE drafted the manuscript, all authors contributed significantly to study design and concept, all authors reviewed the manuscript for important intellectual content.

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Declaration of Competing Interest

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